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Moderate and severe neutropenia in patients with systemic lupus erythematosus

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Objectives. **Neutropenia is an uncommon albeit relevant finding in patients with systemic lupus erythematosus (SLE). It has been ascribed to several aetiologies and represents a challenging dilemma in which clinical findings, laboratory data and medication history must be carefully evaluated. The aim of this work was to review the cases of moderate and severe neutropenia in our cohort of SLE patients in order to identify predisposing factors, clinical outcomes and related prognostic implications.**

Methods. **Thirty-three cases of neutropenia (neutrophil count <1000/μl) in patients with SLE were included. Sixty-five age- and sex-matched patients with SLE served as controls. Information was obtained by medical chart review. Statistical analyses included descriptive statistics, Student's *t*-test, paired *t*-test, χ^2 or Fisher's exact test, and logistic regression.**

Results. **Baseline characteristics did not differ between groups. Use of concomitant medications and immunosuppressive drugs, as well as history of thrombocytopenia and central nervous system involvement, were associated with an increased risk for developing neutropenia. Along with neutropenia, cases had lower haemoglobin and platelet values and higher levels of liver enzymes. Moreover, disease activity was lower than in controls. One month after the neutropenia event, leucocyte and total granulocyte counts were still lower in patients than in controls. Mortality did not differ between patients with neutropenia and controls.**

Conclusions. **Most episodes of severe granulocytopenia in SLE patients occur as part of drug toxicity-induced medullar hypoplasia.**

KEY WORDS: Granulocytopenia, Neutropenia, Systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with highly heterogeneous clinical manifestations. Haematological anomalies that include varying degrees of anaemia, leucopenia and thrombocytopenia are commonly found. Nevertheless, in the setting of SLE, cytopenias may be due to several aetiologies. Disease activity, bone marrow failure, drug toxicity, peripheral destruction, tumour infiltration and sepsis have all been implicated [1, 2].

Even though neutropenia has been reported to occur as a consequence of disease activity (probably related to anti-granulocyte antibodies) [3], several potential causes of such abnormality are frequently found. Interestingly, a positive correlation has been found between high neutrophil clustering activity (NCA) and low peripheral neutrophil count; likewise, high NCA has been related to SLE activity. Whether this parameter will help to discriminate between cytostatic drug-induced cytopenia, SLE-induced cytopenia and the formation of intravascular leucoaggregates remains to be proven [4, 5]. Another factor worth considering is that many patients with SLE have been exposed to alkylating drugs, which have been related to the development of myelodysplastic syndromes and secondary acute leukaemias [6]. Therefore, although frequently encountered in clinical practice, cytopenias in patients with SLE represent a challenging dilemma in which physicians must carefully evaluate clinical findings and laboratory data, as well as present and past medication. Hence, a bone marrow aspirate and core biopsy are often required to elucidate the cause of cytopenias in the background of SLE.

Due to inherent immune abnormalities and the immunosuppressive treatment they are exposed to, patients with SLE are highly susceptible to infection [7]. The relationship between neutrophil count and infection in patients with SLE is not well established. Surprisingly, although low serum levels of soluble Fc-γ receptor and high levels of granulocyte colony-stimulating factor (G-CSF) have been recognized as risk factors for developing infection in patients with SLE and neutropenia, absolute neutrophil count, bone marrow findings, measurements of the marrow neutrophil reserve and serum levels of neutrophil granule components have not [8–10].

The present work focuses specifically in neutropenia, an infrequent finding in patients with SLE. In a prospective study that included 126 patients with SLE, moderate and severe neutropenia (less than 1000 and 500 polymorphonuclear leucocytes/μl, respectively) was reported in approximately 5% [11].

In summary, neutropenia is an uncommon, albeit relevant, finding in patients with SLE that has been ascribed to several aetiologies, and represents a complex clinical problem. The aim of this work was to review the cases of moderate and severe neutropenia in our SLE population, emphasizing disease activity, drug associations and infectious complications, in order to identify predisposing factors, clinical outcomes and related prognostic implications.

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TABLE 1. Demographic characteristics of study population

	SLE patients		
	With neutropenia, $n=33$	Without neutropenia, $n=65$	P
Age at hospitalization[a] (yr)	28.0 ± 10.0	28.4 ± 9.6	0.85
Gender (F/M)	31/2	62/3	1.00
Body mass index[a]	23.9 ± 6.4	23.8 ± 4.0	0.88
Smoking (ever)	21.2%	33.8%	0.19

[a]Mean ± S.D.

Patients and methods

The present study was approved by the Institutional Committee on Biomedical Research. Due to the retrospective and anonymous nature of the study, informed patient consent was not required.

Patients

We identified all SLE patients who fulfilled the American College of Rheumatology classification criteria [12] and were hospitalized between 1984 and 2002 at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) with moderate or severe neutropenia (less than 1000 and 500 neutrophils/μl, respectively). For each case, two SLE patients, matched by age (±5 yr) and gender, hospitalized during the same period (±1 month), for any reason except neutropenia, were selected as controls.

Collected data

Sociodemographic and behavioural data were collected from medical charts using a standardized format. Emphasis was made on SLE course, including the number and type of accrued disease criteria, date of diagnosis (defined as the time when four SLE criteria were met), disease duration (defined as the period of time from SLE diagnosis until index hospitalization), autoantibody profile and treatment (including use of immunosuppressive drugs and concomitant medications). Height and weight during index hospitalization or the closest date were obtained, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres (kg/m^2).

Attention was focused on three different time points: index hospitalization and the two closest medical appointments (prior to and subsequent to index hospitalization). At these dates, information regarding clinical status, laboratory tests, SLE treatment (including immunosuppressive agents and concomitant medications) and disease activity was obtained; bone marrow aspirate and core biopsy were reviewed when available. Disease activity was assessed from medical notes using the SLE Disease Activity Index (SLEDAI) [13] and a validated modified version (Mex-SLEDAI) [14]; chronic damage was determined using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) [15].

Statistical analyses

Continuous variables were analysed using Student's t-test, and categorical variables using χ^2 or Fisher's exact test. The association between neutropenia and diverse variables was estimated by the odds ratio (OR) and 95% confidence intervals (CIs). Clinically relevant variables and variables with a P value ≤ 0.10 were entered into a logistic regression model. The development of neutropenia was considered the dependent variable. Statistical significance was set at a P value ≤ 0.05, two-sided. All analyses were performed using Intercooled STATA, version 7.0 (STATA Corporation, College Station, TX, USA).

Results

Demographic and SLE characteristics

Thirty-three SLE patients (31 female) with moderate or severe neutropenia and 65 SLE controls (62 female) were included. Demographic characteristics were comparable in both groups (Table 1).

The number of SLE criteria accumulated through the disease course was similar in cases and controls (5.2 ± 1.8 *vs* 4.9 ± 1.9). However, neurological criteria (27.2 *vs* 7.6%, $P=0.009$) and thrombocytopenia (33.3 *vs* 21.5%, $P=0.048$) were significantly more common in cases; history of haemolytic anaemia was more commonly reported in patients with neutropenia (15.1 *vs* 7.6%), although the difference did not reach statistical significance ($P=0.06$). The remaining clinical and serological characteristics were similar in both groups (Table 2).

Clinical characteristics prior to the episode of neutropenia

Neutropenic and non-neutropenic patients had been seen 1 month prior to the index hospitalization. At that visit, disease activity was similar in both groups (SLEDAI 5.2 ± 6.5 *vs* 6.9 ± 5.6; Mex-SLEDAI 3.8 ± 4.9 *vs* 5.4 ± 3.9). Interestingly, patients who would develop neutropenia had higher values of mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) (Table 3). With regard to treatment, the use and dose of corticosteroids was similar in both groups. No single immunosuppressive drug was significantly associated with the development of neutropenia. Nevertheless, a non-significant tendency towards a higher use of methotrexate in patients with neutropenia was observed. When the use of any immunosuppressive drug was considered as an independent variable, once more, in the univariate analysis only a trend was observed towards a more frequent use of these drugs in patients who would develop neutropenia (60.6 *vs* 44.6%, $P=0.13$; Table 4). Use of non-steroidal anti-inflammatory drugs (NSAIDs) was similar in both groups (data not shown).

Use of concomitant medications prior to the development of neutropenia

Concomitant medication was defined as any drug other than corticosteroids, immunosuppressive agents or NSAIDs taken continuously during at least 2 weeks during the month prior to the event of neutropenia. In the univariate analysis, the use of both cisapride and phenytoin was found to be significantly higher amongst patients within the neutropenia group ($P=0.04$ and 0.02, respectively). Also, a non-significant trend was observed with amoxicillin-clavulanic acid and trimethoprim-sulphamethoxazole (Table 4). However, in the multivariate analysis no single

Table 2. Clinical and serological characteristics of SLE in the study population

	SLE patients		
	With neutropenia, $n=33$	Without neutropenia, $n=65$	P
SLE criteria[a]	5.2 ± 1.8	4.9 ± 1.9	0.57
Age at SLE diagnosis[a] (yr)	25.9 ± 10.6	25.7 ± 10.1	0.92
Disease duration[a] (yr)	2.2 ± 2.7	3.1 ± 3.6	0.22
Length of follow-up[a] (yr)	2.5 ± 4.2	2.6 ± 3.9	0.85
Neurological criteria, *n* (%)	9 (27.2)	5 (7.6)	0.009
Thrombocytopenia, *n* (%)	11 (33.3)	14 (21.5)	0.048
Haemolytic anaemia, *n* (%)	5 (15.1)	5 (7.6)	0.06
SLICC/ACRDI score[a] (first visit)	0.18 ± 0.59	0.12 ± 0.54	0.57
AAN, *n* (%)	22 (81.8)	35 (89.5)	0.50
Anti-dsDNA, *n* (%)	17 (73.9)	34 (87.1)	0.48
Anticardiolipin antibodies, *n* (%):			
IgG	4 (23.5)	9 (32.1)	0.59
IgM	9 (52.9)	11 (39.2)	0.48
Decreased complement levels, *n* (%):			
C3	13 (61.9)	23 (62.1)	0.81
C4	13 (68.4)	32 (86.4)	0.27

[a]Mean ± S.D.

Table 3. Disease activity and laboratory parameters prior to and during the development of neutropenia

	Prior to neutropenia			Episode of neutropenia		
	With neutropenia	Without neutropenia	P	With neutropenia	Without neutropenia	P
SLEDAI	5.2 ± 6.5	6.9 ± 5.6	0.27	5.8 ± 4.7	9.8 ± 6.7	0.001
Mex-SLEDAI	3.8 ± 4.9	5.4 ± 3.9	0.15	3.8 ± 3.4	6.4 ± 4.3	0.002
Infection (%)	–	–	–	75.7	49.2	0.012
Haemoglobin	11.6 ± 2.6	11.5 ± 2.3	0.87	8.9 ± 2.4	11.1 ± 2.4	<0.001
Leucocytes	5908 ± 3368	5925 ± 2942	0.98	1071 ± 654	8832 ± 4692	<0.001
Neutrophils	3793 ± 2627	4162 ± 2336	0.56	307 ± 253	7003 ± 4134	<0.001
Lymphocytes	948 ± 706	1143 ± 768	0.30	627 ± 616	1165 ± 979	<0.001
Platelets	224 ± 104	249 ± 142	0.44	138 ± 111	236 ± 145	0.001
MCV	89.1 ± 8.1	85.1 ± 7.2	0.04	89.18 ± 7.8	86.6 ± 7.1	0.12
MCH	30.4 ± 3	28.7 ± 3.1	0.04	30.5 ± 3.7	29.8 ± 3.1	0.33
SGOT	60.4 ± 145	45.1 ± 66.8	0.65	95.1 ± 151.3	42.7 ± 50.9	0.02
SGPT	53.8 ± 117	30.6 ± 40.8	0.38	83.3 ± 141.4	34.9 ± 46.5	0.02

MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; SGOT, serum aspartate aminotransferase; SGPT, serum alanine aminotransferase.

medication reached a significant level of association with the presence of neutropenia. Nonetheless, when considered as a whole, the use of any concomitant medication was more common in cases than in controls (58 *vs* 20%, $P<0.001$) and it was associated with a high risk for developing neutropenia (OR 16.5, 95% CI 2.9–94.4; Tables 4 and 5).

Clinical characteristics during hospitalization

During hospital admission, infection was detected in a higher proportion of patients with neutropenia than in controls (75.7 *vs* 49.2%, $P=0.012$). Conversely, disease activity scores were significantly lower in cases than in controls (SLEDAI 5.8 ± 4.7 *vs* 9.8 ± 6.7, $P=0.001$; Mex-SLEDAI 3.8 ± 3.4 *vs* 6.4 ± 4.3, $P=0.002$).

Besides total leucocyte and neutrophil counts, lymphocyte count was lower in neutropenic patients than in controls (627 ± 616 *vs* 1165 ± 979, $P<0.001$). Likewise, haemoglobin and platelet levels were lower in neutropenic patients (haemoglobin 8.9 ± 2.4 *vs* 11.1 ± 2.4, $P<0.001$; platelets 138 ± 111 *vs* 236 ± 145, $P=0.001$). In addition, serum aminotransferases were elevated in cases [SGOT (serum aspartate aminotransferase) 95.1 ± 151.3 *vs* 42.7 ± 50.9, $P=0.02$; SGPT (serum alanine aminotransferase)

Table 4. Use of prednisolone, immunosuppressants and concomitant medications prior to the development of neutropenia

Corticosteroids and immunosuppressive drugs	With neutropenia	Without neutropenia	P
Prednisolone	78.1%	80.0%	0.83
Prednisolone (mg) (mean daily dose)	28.19 ± 26	24.38 ± 21.3	0.44
Azathioprine	36.3%	40.0%	0.73
Azathioprine (mg) (mean daily dose)	91.6 ± 35.8	83.6 ± 34.5	0.52
Cyclophosphamide p.o.	3.0%	1.5%	0.56
Cyclophosphamide i.v.	18.1%	10.7%	0.31
Methotrexate	9.1%	1.5%	0.07
Any immunosuppressive drug	60.6%	44.6%	0.13
Concomitant medications			
Acyclovir	6.1%	1.5%	0.21
Allopurinol	3.0%	1.5%	0.62
Amoxicillin–clavulanic acid	9.1%	1.5%	0.07
Cisapride	6.1%	0	0.04
Phenytoin	12.1%	1.5%	0.02
Omeprazol	6.1%	1.5%	0.21
Trimethoprim–sulphamethoxazole	9.1%	1.5%	0.07
Any concomitant medication	58%	20.0%	0.001

TABLE 5. Variables associated with the development of neutropenia in SLE patients

Variables	OR (95% CI)	*P*
Use of immunosuppressive drugs	4.81 (1.1–20.8)	0.035
History of CNS involvement	5.04 (1.2–20.8)	0.025
History of thrombocytopenia	4.72 (1.8–12.6)	0.002
Use of concomitant medications	16.5 (2.9–94.4)	0.002

83.3 ± 141.4 *vs* 34.9 ± 46.5, $P = 0.02$] (Table 3). No differences in renal function tests, antinuclear antibodies or complement levels were detected (data not shown).

Bone marrow aspirates

A bone marrow aspirate was performed in 14 cases. Cellularity was diminished in six patients, normal in five, increased in two and could not be evaluated in one. Two patients showed myeloid hyperplasia. Megakaryocytes were increased in one case and decreased in two. Twelve patients showed changes consistent with drug-induced marrow toxicity (granulocytic maturation arrest at myelocyte stage, increase in eosinophils and dyserythropoiesis).

Outcome

The mean duration of neutropenia was 14.3 ± 14 days; in nine cases G-CSF was used. One month after the episode of neutropenia, total leucocyte and neutrophil counts remained lower in cases than in controls (leucocytes 4546 ± 1592 *vs* 7421 ± 3022, $P < 0.001$; neutrophils 2812 ± 1381 *vs* 5263 ± 2377, $P < 0.001$). There were no differences in new hospital admissions within the next month following the neutropenia episode.

During hospitalization one death occurred in the control group and two among the cases (only one directly related to neutropenia).

Multivariate analysis

The following variables were identified as independently associated with the development of neutropenia: use of immunosuppressive drugs (OR 4.81, 95% CI 1.1–20.8), history of central nervous system manifestations (OR 5.04, 95% CI 1.2–20.8), history of thrombocytopenia (OR 4.72, 95% CI 1.8–12.6) and use of concomitant medications (OR 16.5, 95% CI 2.9–94.4) (Table 5). The interaction between immunosuppressive drugs and concomitant medication was not significant.

Discussion

In this study, we analysed the clinical and laboratory characteristics of 33 patients with SLE who developed neutropenia. History of thrombocytopenia and central nervous system (CNS) activity, as well as use of immunosuppressive and concomitant medications, were identified as independent risk factors for the development of neutropenia. Thus, our results suggest that, in patients with SLE, drug toxicity rather than disease activity is the most common aetiology of neutropenia.

Leucopenia, first reported by Goeckerman in 1932 [11], is a common finding in patients with SLE. As expected, in their series, low leucocyte counts were primarily due to lymphopenia, whilst neutrophil numbers were usually normal. Likewise, Michael found that although 14% of untreated SLE patients had leucocyte counts lower than 2000, only 2% had neutrophil counts below 1000 [16]. Alarcón-Segovia reported a patient with SLE who simultaneously developed severe neutropenia and Coombs positive haemolytic anaemia while receiving prymidone; both resolved after the interruption of the drug [17]. Deleze *et al.* found a direct relationship between anti-phospholipid antibodies (APLA) and history of leucopenia in patients with SLE; although they suggested APLA might be related to neutropenia in SLE patients, their data were not conclusive [18]. This information has indirectly dealt with the issue but, to the best of our knowledge, no reported series has specifically focused on neutropenia in patients with SLE.

In the present study, cases were compared against a robust number of controls, matched by age, gender and hospitalization date. Cases and controls comprised homogeneous and thus comparable groups. This fact is well portrayed in Tables 1 and 2, where no differences in demographic or SLE-related data were found. When we compared the two groups, we found that patients who developed neutropenia had a significantly higher frequency of CNS and haematological activity than patients in the control group. This, in addition to a higher exposure to immunosuppressive agents and other drugs (referred to here as concomitant medications), was significantly associated with the development of neutropenia (Table 5). It may be argued that cases comprised a group of patients with a more severe disease than controls. However, disease activity and damage scores were similar in both groups 1 month prior to the event (Tables 1 and 2). Further, it is important to emphasize that other severe disease manifestations, such as glomerulonephritis, that entail the use of intense immunosuppression were not associated with the development of neutropenia. Thus, data do not support the notion that neutropenia was due simply to immunosuppressive drug-induced bone marrow toxicity, but was probably a consequence of a combination of factors including concomitant medication and perhaps disease-related marrow damage.

The only differences between cases and controls 1 month prior to the development of the neutropenic episode was that cases exhibited higher median corpuscular volume and mean corpuscular haemoglobin. Such differences may represent initial toxicity-related changes, apparent before overt abnormalities were detectable. During the episode of neutropenia, laboratory abnormalities associated with drug toxicity were conspicuous. Along with neutropenia, leucopenia, lymphopenia, thrombocytopenia and anaemia were present. Further, serum aminotransferases were elevated in cases when compared with controls. These findings are congruent with each other and with those reported in bone marrow, where toxicity-related anomalies were evident in most cases. Thus, bone marrow failure, probably related to medication, was responsible for the cytopenia observed in most patients. Such a notion was further supported by the results of the multivariate analysis. Along with history of thrombocytopenia and CNS activity, the use of immunosuppressive drugs, as well as the use of concomitant medications, imposed the strongest risk for the development of neutropenia.

In two cases (out 14 available aspirates), the bone marrow aspirate exhibited myeloid hyperplasia. Although such a finding is not specific (it may be found in patients exposed to drugs, infection or in antibody-mediated neutropenia), it suggests that neutropenia was not due to marrow failure. It is thus possible that in those cases neutropenia was caused by SLE activity. Nevertheless, neither activity scores nor disease activity-associated clinical or laboratory findings differed in those two patients when compared with the patients with marrow-toxicity induced neutropenia (data not shown). This fact underscores the value of the bone marrow aspirate in patients with SLE who develop neutropenia, where no other clinical or laboratory finding is able to distinguish between SLE activity and marrow toxicity-induced cytopenia. At this point it is important to emphasize that in less than 10% of the patients disease activity was identified as the probable cause of neutropenia. This may be due to several factors. The patients described were all under medical treatment at the time of the

neutropenia event. Further, they were identified during a hospital admission, which imposes an obvious selection bias in the study population. More than 75% of them had an infectious process. Thus, the event of neutropenia they underwent was probably more severe or protracted than the cases seen on a daily basis that spontaneously recover, without the need for hospital management. Further, the most important drawback of the study, its retrospective design, must be considered. It imposes obvious limitations in the information-gathering process. Thus, some data such as serology could only be partially obtained.

We believe that our results stress the importance of cautious use of medication in patients with SLE; they highlight that only essential drugs should be used, because the addition of seemingly innocuous medicines might trigger an event of neutropenia in these patients [19]. Moreover, although our study did not consider patients with other autoimmune diseases, it is reasonable to consider that patients who receive immunosuppressive drugs for other reasons might be at risk of developing neutropenia in analogous scenarios.

Based on the results of this study, we may conclude that most episodes of severe granulocytopenia in SLE patients occur as part of drug toxicity-induced medullar hypoplasia.

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